

EP-1160

Increasing radiotherapy responsiveness of mesothelioma by activating tumour specific cell death

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Purpose/Objective: Mesothelioma is a radioresistant cancer and around 80% of the cases occur due to asbestos exposure. The incidence of mesothelioma is increasing and current treatments are ineffective. While advances in technical radiotherapy are increasing its potential clinical application, the intrinsic radiation resistance of mesothelioma remains an important barrier. Defects in the apoptosis pathway are a likely cause of radioresistance and treatment with Tumour necrosis factor-Related Apoptosis Inducing Ligand (TRAIL) has potential to overcome this.

Materials and Methods: Radiation and TRAIL (*iso-leucine zippered* form) were tested alone and in combination in mesothelioma cell lines MSTO-211H and H2052 to determine effects on cell viability, clonogenic survival and apoptosis (measured by caspase-3/7 activity and Annexin-V/PI analysis). Cell surface and total levels of the death receptors DR4 and DR5 were also analysed to investigate potential mechanisms underlying interactions between radiation and TRAIL.

Results: Radiation and TRAIL exhibit schedule-dependent synergy. Addition of TRAIL 24 hours post radiation was associated with significant increases in apoptosis and reductions in cell viability and clonogenic survival in both cell lines. Radiation caused upregulation and externalisation of DR4 & DR5 with maximum effects 24 hours after radiation. We hypothesised that radiation induces DR4/5 upregulation and externalisation enabling activation of the extrinsic apoptotic pathway by TRAIL. This was verified by showing that inhibition of the extrinsic apoptotic pathway blocked the cytotoxic effects of the radiation/TRAIL combination whereas inhibition of the intrinsic pathway did not.

Conclusions: Use of TRAIL in combination with radiation overcomes radioresistance exhibited by mesothelioma cells. The synergistic combination of TRAIL and radiation has therapeutic potential in mesothelioma.

EP-1161

Staging FDG PET/CT is not an adequate baseline for quantitative metabolic monitoring of (chemo)radiation for NSCLC

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Purpose/Objective: FDG PET/CT has become a routine diagnostic instrument for staging and treatment planning of NSCLC. There is an increasing interest in quantitative metabolic evaluation of FDG PET as an early marker of response during and shortly after treatment. Routine diagnostic FDG PET/CT scans that were performed for staging purposes are often used at baseline for standardized uptake value (SUV) measurements. However, a diagnostic scan may be suboptimal for this purpose for several reasons, e.g. it may be relatively old, not in treatment position, or acquired with equipment with different characteristics compared to the one used for response evaluation. We hypothesized that a separate baseline FDG PET/CT at the start of treatment may provide more reliable response monitoring.

Materials and Methods: We included 13 patients with proven NSCLC, who were referred for curative intent concurrent chemoradiation (CCRT) in an ongoing prospective trial for quantitative evaluation of tumor metabolism during treatment. All patients had already received a routine FDG PET/CT in the diagnostic work-up (PET1), and underwent a 2nd scan in the morning prior to fraction 1 (PET2). Noted were the interval between PET1 and start of treatment, FDG biodistribution time, SUV_{max} of the primary tumor, and whether PET1 was performed in a different center or with a different scanner brand than PET2. All applied scanners were calibrated for SUV measurements using standard quality assurance procedures.

Results: Significant time intervals with mean 38 days (range 20-60) occurred between PET1 and start of treatment (PET2). FDG biodistribution times were comparable with mean 68 minutes for both PET1 and PET2, although deviations were slightly larger for PET1 (range 53-107 minutes, versus 54-91 for PET2). SUV_{max} values showed large differences between PET1 and PET2 (absolute mean +29%, range -35-+84%). None of the PET1 scans were performed in treatment position. The patients who had both scans acquired on the same scanner brand (Philips TF) generally showed SUV_{max} progression before the start of treatment (mean +33%, range -11-+84%), consistent with assumed variable tumor progression. However, most patients with a baseline scan acquired using a different scanner brand (all Siemens) showed a lower SUV_{max} at the start of treatment (mean -14%, range -34-+10), indicating a significant quantification issue despite all scanners being calibrated for SUV. One patient showed progression to stage IV on PET2 (with an interval of 48 days with PET1), leading to change of management.

Conclusions: SUV quantification using a routine staging FDG PET/CT may deviate significantly from measurements at the start of treatment, with differences up to 84% that were apparently caused by tumor progression, positioning differences and application of different scanner brands. A baseline PET shortly before treatment on the same scanner brand is recommended for quantitative monitoring of metabolic parameters during (chemo)radiotherapy for NSCLC to avoid misinterpretation of signal changes.

EP-1162

Internal Target Volume interfraction changes and dose coverage in Stereotactic Body Radiotherapy for lung tumors

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